Santa Barbara County
PUBLIC Health
DEPARTMENT

EMERGENCY MEDICAL SERVICES AGENCY
300 North San Antonio Road
Santa Barbara, CA 93110-1316
805/681-5274 FAX 805/681-5142

AN EVALUATION OF ONDANSETRON FOR UNDIFFERENTIATED NAUSEA AND VOMITING IN THE PREHOSPITAL AND INTERFACILITY TRANSFER SETTING

Report to the California Commission on EMS

June 24, 2009

Angelo Salvucci, MD, Santa Barbara County EMS
Marc Burdick, EMT-P, Santa Barbara County EMS
Mark Luoto, MD, Coastal Valleys EMS
Reza Vaezazizi, MD, Inland Counties Emergency Medical Agency
David Brazzel, MD, El Dorado County EMS
Benjamin Squire, MD, Harbor UCLA Emergency Medicine

Table of Contents

1. Acknowledgements

This ondansetron trial study was made possible through extensive cooperation from four (4) EMS Agencies covering eight (8) California counties. We wish to express our appreciation and gratitude to the following individuals who helped make this study possible through their support and participation in the project.

Santa Barbara County		
Les Hugie, EMT-P	Clinical Education Specialist	AMR – Santa Barbara
Inland Counties EMS Agency		
Sherri Shimshy, RN	Nurse Specialist	Inland Counties EMS
Iris Pena, RN	Nurse Specialist	Inland Counties EMS
Coastal Valleys EMS Agency		
James Salvante, EMT-P	ALS Coordinator	Coastal Valleys EMS
El Dorado County EMS Agency		
Brian Bresnahan, EMT-P	Program Coordinator	El Dorado County EMS

2. Abstract

Objectives: The primary objective was to evaluate the safety and efficacy of ondansetron in the out-of-hospital treatment of undifferentiated nausea or vomiting. The secondary objective was to explore the utility of an online database in the coordination of a multi-site study group.

Methods: EMS patients in eight California counties with severe nausea or intractable vomiting were treated with intravenous, intramuscular, or oral ondansetron, without online medical control. Data were collected prospectively for a 6-month period using an online database. Outcome measures were: 1) efficacy as measured by a verbal quantitative nausea scale and 2) incidence of adverse effects. There were no control or placebo groups.

Results: Ondansetron was administered to 2071 patients (~3.1% of all patients transported during the study period). Overall the mean decrease in nausea score was 3.99 on a 10 point scale. After medication administration, four patients had mild hypotension, one had hypertension, two had itching or rash, and one had a brief episode of supraventricular tachycardia that resolved spontaneously. The online database system was effective in allowing for universal accessibility, ease of data entry, and availability for monitoring and analysis, and enabled a uniform and consistent quality improvement process.

Conclusions: Ondansetron is safe and effective in the out-of-hospital treatment of nausea and vomiting. Given the prevalence and degree of discomfort of this condition, ondansetron should be added to the statewide paramedic scope of practice and its use widely encouraged. The online database method of data collection and analysis was highly effective and its expanded use should be facilitated by the EMS Authority to support other statewide EMS CQI projects, studies, and data collection.

3. Introduction

Nausea and vomiting are common patient complaints in emergency medical services systems, both prehospital and during interfacility transfers. Though not well-studied, one report found that 5% of prehospital patients required treatment.[1] Nausea is often a significant concern, and many patients consider nausea to be a more uncomfortable symptom than pain.[2] In California, the paramedic scope of practice does not address this well. Diphenhydramine may be used as an antiemetic, but is rarely used for that purpose in the emergency department, and causes drowsiness. A previous California EMS trial study on the treatment of motion sickness with diphenhydramine (Benadryl®) or metoclopramide (Reglan®) was terminated in 2008, and with a limited number of enrolled patients no addition to the paramedic scope of practice was recommended.

Ondansetron (Zofran®) is a widely used antiemetic agent in the hospital and in outpatient settings. It has been used safely and effectively for the treatment of undifferentiated nausea and vomiting in emergency department and emergency medical services settings.[1,3-8] It is used in a number of EMS jurisdictions outside California. As the cost of the medication has declined to less than $1.00 per dose, ondansetron is an attractive option in prehospital and interfacility transfer care.

On 21 August, 2008, the Santa Barbara County Emergency Medical Services (EMS) Agency submitted a Trial Study request with the California EMS Authority to evaluate the utilization, safety, and efficacy of ondansetron in the out-of-hospital setting. On 20 October, 2008, Dr. Tharratt approved the trial study for a period of eighteen (18) months. Coastal Valleys EMS Agency, Inland Counties EMS Agency (ICEMA), and El Dorado County EMS Agency were also approved to participate. Approval and EMS Commission dates are listed in Table 1.

Table 1: Participating EMS Agencies and Counties

EMS Agency	County(ies)	Approval Date	EMS Commission Notification
Santa Barbara	Santa Barbara	10/20/08	12/3/08
Coastal Valleys	Napa Sonoma Mendocino	10/20/08	12/3/08
Inland Counties	San Bernardino Inyo Mono	10/21/08	12/3/08
El Dorado	El Dorado	3/25/08	3/25/09

Interim trial results were presented to the EMDAC Scope of Practice Committee and Dr. Tharratt on March 24, 2009. Based on that discussion it was agreed that sufficient data would be available before the 18 month approval period was complete and that the trial results would be presented for analysis and action at the June 2009 EMDAC Scope of Practice and EMS Commission meetings.

4. Methods

Study Design

This was a prospective, observational study with the objective of evaluating the utilization, safety and efficacy of the out-of-hospital administration of intravenous, intramuscular, and oral ondansetron in the treatment of undifferentiated nausea or vomiting. There were no control or placebo groups. Paramedic treatment protocols were modified so that all patients without a contraindication who met clinical criteria were candidates to receive the medication.

Setting

The trial study took place simultaneously in four EMS Agencies comprising 8 counties: Santa Barbara County, Inland Counties EMS Agency (ICEMA - San Bernardino, Inyo, and Mono Counties), Coastal Valleys EMS Agency (CVEMSA - Napa, Sonoma and Mendocino Counties) and El Dorado County. Populations and annual call volume are listed in Table 2 below:

Table 2: Participating Counties - Demographics

County	Population[1]	Size (sq mi)[1]	EMS (ALS & BLS)[2]	IFT[2]
Santa Barbara	425,710	2737	30,500	4500
San Bernardino	2,015,355	20,052	165,478	53,554
Inyo	17,136	10,203	1823	187
Mono	12,774	3044	1429	45
Napa	133,433	754	5,492	n/a
Sonoma	466,741	1576	30,639	n/a
Mendocino	86,221	3509	5,041	n/a
El Dorado	176,075	1711	12,417	1705

1: Source; US Census Bureau, 2008 Estimate

2: Source: Local EMS Agency for respective county

Experimental Protocol

The trial study began in Santa Barbara County on December 15, 2008 and by mid-March 2009 all jurisdictions were participating.

Paramedics were provided a 90-minute training program, facilitated by their local service provider's education program (or base hospital), consisting of a PowerPoint® presentation, demonstration, skill competency and written examination. The curriculum included drug pharmacology, patient selection, and the nausea scale. (Appendix A)

A standardized protocol was implemented that allowed paramedics to administer ondansetron without online medical control (Appendix B). Inclusion criteria were: 1) age 4 years or greater, and 2) severe nausea or intractable vomiting. Exclusion criteria (contraindications) were known sensitivity to drugs of the same class as ondansetron (5-HT3 antagonists). The preferential route was intravenous. Patients without an IV were given the medication IM or PO (oral-dissolving tablet – ODT). Route was selected by the paramedic with assistance of the base hospital where local protocol required. The dose was 4 mg IV/IM/PO for all ages (4 years or greater). A single repeat dose was allowed in the protocol under standing orders or with online medical control. A third dose required online medical control orders.

Outcome Measures

The primary outcome measures were the change in nausea as reported by the patient and any adverse effect experienced by the patient after administration of ondansetron. A 10-point verbal quantitative scale was prepared (*Figure 1*) and used before and after each dose of the medication. The verbal scale was taken from the work of Craig Warden, MD (personal communication, [1])

The special nausea visual analog scale (VAS) was developed to evaluate patient comfort and status prior to and following every ondansetron administration. This 10-point scale was used by paramedics and their patients to quantitatively evaluate the patient's level of distress and track any improvement in the patient's status. All patients with adverse or untoward effects were identified by both the treating paramedic and during the clinical review of each case. All possible adverse reactions were reviewed by the provider medical director and these data were entered into the online data tool.

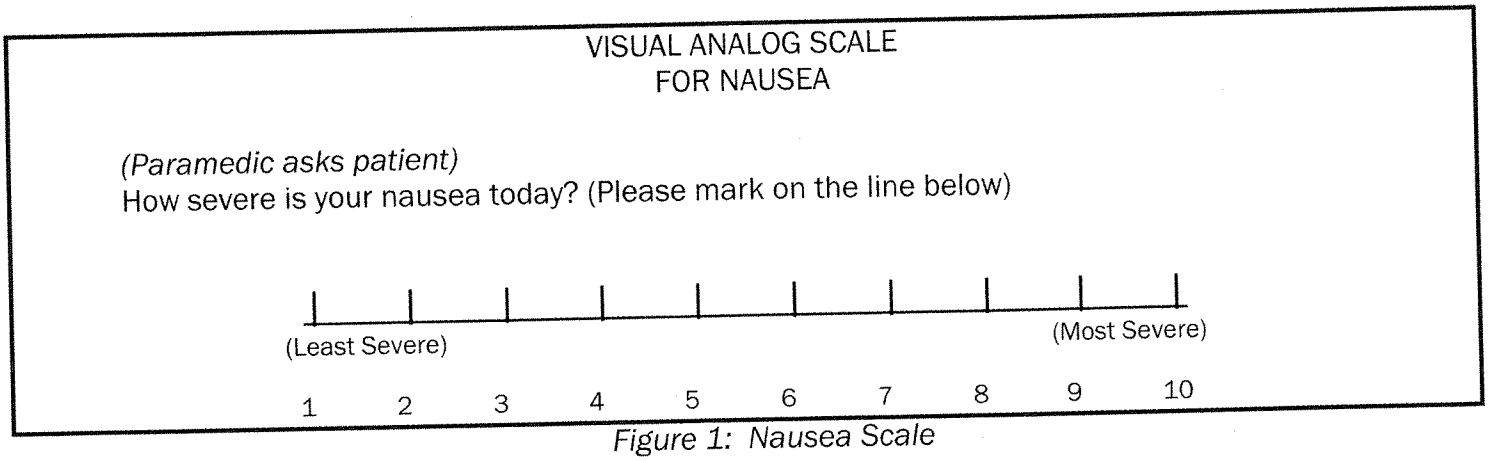


Figure 1: Nausea Scale

Medical Oversight

Paramedics were required to successfully complete a training session and pass a post-course examination before being authorized to administer the medication. A quality improvement /data collection form was completed after all uses (Appendix C), and these were reviewed by a quality improvement coordinator. All unusual events were reviewed by the medical directors of the ALS provider and LEMSA.

Data Collection

Data was collected using a structured data collection form designed by the investigators. After each patient contact in which ondansetron was administered, the treating paramedic completed a data collection form and/or electronic patient care record (PCR). These forms were reviewed by the provider CQI coordinator and verified against the PCR. If discrepancies were present, the prehospital care report was used. After verification, deidentified data from the forms were entered by CQI coordinators into an online electronic database, SurveyMonkey.com (www.surveymonkey.com). See Appendix D.

Data from the electronic online database was downloaded as an Excel spreadsheet (Microsoft, Inc., Redmond WA) and imported into STATA/IC 10.1(STATA Corporation, College Station, TX) for analysis.

Statistical Methods

Exact confidence intervals for the mean change in nausea score were calculated and P-values for the changes were calculated using the Wilcoxan sign rank test. Differences in improvement of nausea scores by route of administration were compared by multivariate regression.

5. Results

All eligible patients transported between December 15, 2008 and May 15, 2009 were included. Data were submitted for 2072 subjects. All 2072 records had complete premedication and postmedication nausea scores. The intent to treat analysis included 2001 subjects who received one dose, 70 subjects who received two doses and one subject who did not receive any medication. Subjects with an initial nausea score of zero (cases in which ondansetron was given prophylactically) were excluded from the effectiveness analysis but were included in analysis of adverse events.

Subject ages ranged from 2 years old (out of protocol, interfacility transfer with physician order) to 100 years old. 66 subjects were less than 18 years old, 17 less than 13 years old, and three were 6 years old and younger. The full age fractal analysis is show in Figure 2 below. 64% of subjects were female and 36% were male (*Figure 3*)

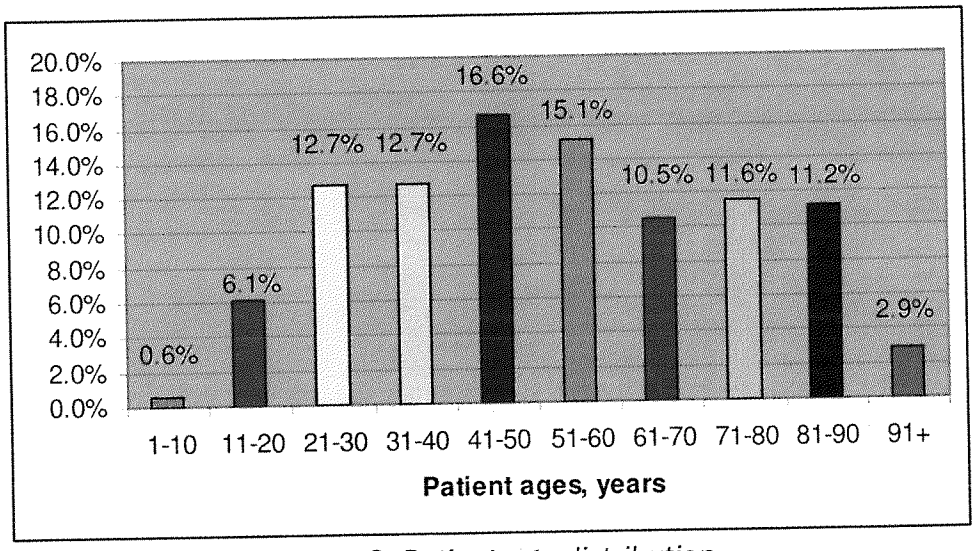


Figure 2: Patient age distribution

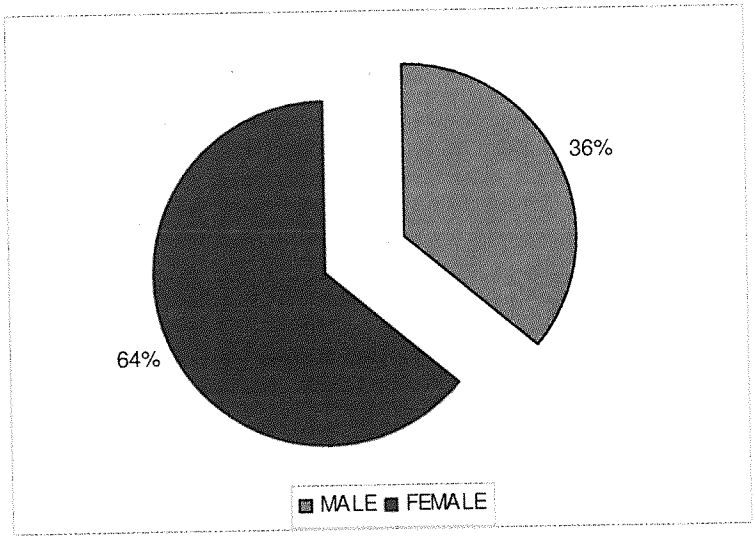


Figure 3: Gender distribution

1321 subjects (64%) received ondansetron IV, 77 (4%) received ondansetron IM, and 674 (33%) received ODT (*Figure 4*). Initial dose was 4mg for all IM and ODT administrations and for all except 3 IV administrations. Three adult subjects received a 2mg IV dose and one two-year-old subject received a 1mg IV dose. The lower doses were given with medical control order and were included in all analyses.

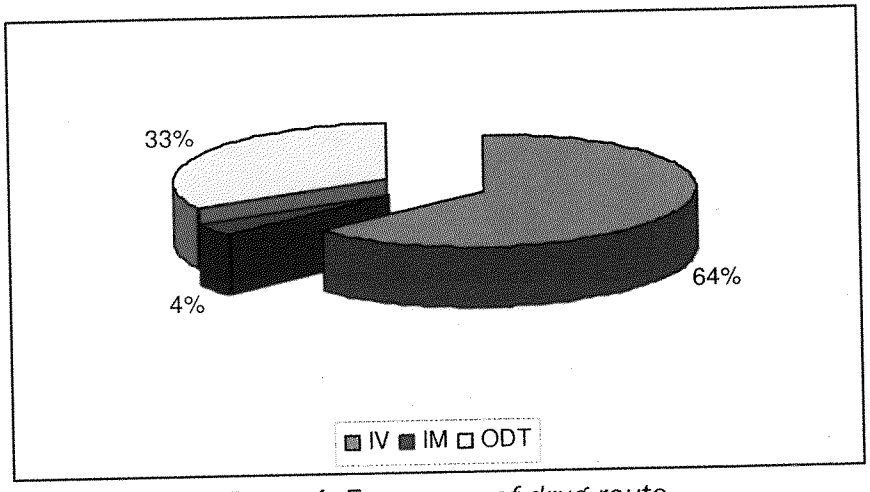


Figure 4: Frequency of drug route

Of 2053 subjects with nausea, 1634 (80%) had improvement of their nausea after the medication, 395 (19%) had no change in nausea after the medication and 24 (1%) had worsening of their nausea after the medication. For all patients with nausea, the nausea score declined from a pre-administration mean of 7.69 to a post-administration mean of 3.70, for a mean improvement of 3.99 (95%CI 3.82, 4.08, $p<0.001$). In patients who improved, the mean improvement in nausea score was 5.05 (95%CI 4.94, 5.17, $p<0.001$).

IV administration resulted in the largest improvements in nausea scores (mean 4.36, 95%CI 4.15, 4.37), followed by IM (mean 3.61, 95%CI 2.95, 4.27) and ODT (mean 3.28, 95%CI 3.06, 3.50) (*Figure 5*). Difference IV vs. IM = 0.70, p=0.043. Difference IM vs ODT = 0.33, p=0.353. Difference IV vs. ODT 1.03, $p<0.001$.

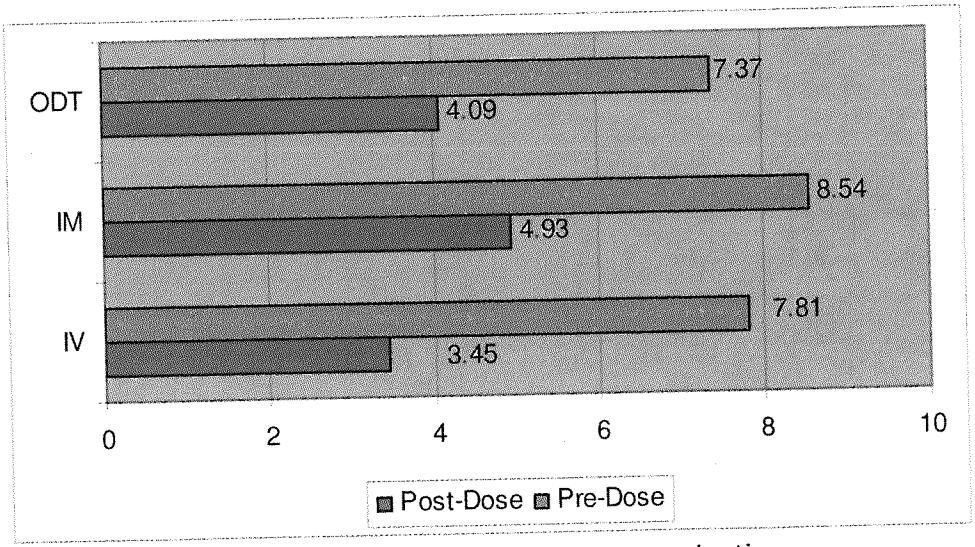


Figure 5: Route-related nausea reduction

Seven prehospital (no IFT) patients (0.3% of the total) had post- administration changes that were evaluated as potential adverse medication reactions (Table 3). There were four episodes of hypotension, all mild, three of which were in patients who were vomiting. There was one episode of hypertension. There were two histamine-related episodes, one with localized pruritis and one generalized, neither with changed vital signs. There was one episode of PSVT, in a patient without a history of cardiac dysrhthmias, that resolved before it could be documented and without other findings.

Table 3: Possible Adverse Reactions

Age	M/F	Dose	Route	Synopsis
47	F	4 mg	ODT	Nausea/Vomiting, BP: 118/82 to 86/68
43	F	4 mg	IV	Nausea/Vomiting, B/P 130/94 to 90/60
60	M	4 mg	IV	Nausea, BP 162/145 to 98/57
52	F	4 mg	IV	Nausea/Vomiting, hypotension resolved w/ 400 ml IV NS
88	F	4 mg	IV	Nausea, BP 159/89 to 210/88
25	F	4 mg	IV	Immediate erythema/pruritis at IV site, resolved w/ diphenhydramine
67	F	4 mg	IV	Diffuse pruritis w/o rash
48	F	4 mg	ODT	Transient PSVT at 170 for 5-10 seconds, self-limited

Frequency of Use

To determine overall frequency of use, the cases in the months of March and April were compared to the total number of transported patients (Table 4).

Table 4: Sample Frequency of Use of Ondansetron in March and April 2009

County	Uses	Transports	Ratio (%)
Santa Barbara	85	4528	1.9
Sonoma/Mendocino	193	5228	3.7
San Bernardino	694	15444	4.5
Napa	10	1945	0.5
El Dorado	98	1850	5.3
Inyo	5	238	2.1
Mono	13	139	6.7
Totals/Avg	**1098**	**29426**	**3.7**

6. Selected Case Reports

Case #1

Summary: 18 year-old male fell while skiing and hit his head, no loss of consciousness. The patient got up and started skiing again and subsequently fell again hitting his head a second time. The patient developed moderate nausea, dizziness, and neck pain. He was placed in full spinal precautions and given 4 mg ondansetron IV. His nausea was reduced to mild and stayed controlled without any vomiting throughout the transport.

No negative side effects or reactions were reported.

Case #2

Summary: An 85 year-old male with a chief complaint of severe diarrhea, nausea, and vomiting for two hours. The patient reports severe nausea and was actively vomiting as the paramedics assessed him. He was given 4 mg ondansetron IV and had a rapid improvement with almost no nausea and no vomiting after administration. He remained stable and comfortable for the 30-minute transport on winding mountain roads.

No negative side effects or reactions were reported.

6. Discussion

Ondansetron is safe.
99.7% of the patients receiving ondansetron had no reported adverse reaction. There were a total of seven (0.3% of all patients) possible adverse reactions, all of them mild and transient. Three of the patients who were vomiting became mildly hypotensive, and hypotension is a common finding with vomiting so it is not clear that this was a reaction to the medication. The two allergic reactions and episode of PSVT may have been related to the medication.

Ondansetron is effective. Patients with severe nausea and vomiting appear to benefit from administration of ondansetron by paramedics to reduce their symptoms and increase comfort. The study did not have a control group. Ondansetron has been previously shown to be effective in the treatment of nausea and vomiting in other settings [4-8], and this study was designed to evaluate whether it had a similar effect for out-of-hospital patients. The mean overall reduction in the nausea scale was from 7.69 to 3.70 – for a mean decrease of 3.99. The nausea scale has not been validated and a clinically significant change has not been determined, however for pain the clinically significant threshold (when patients report the pain to be a "little better" or "little worse") has been reported to range from 1.3 to 2.8.[9,10]

IV, IM and PO routes are all effective.
In this population all three routes of administration resulted in a substantial reduction in the nausea scale. The reduction was greatest with the IV route (decrease of 4.36), followed by IM (3.61) then PO (3.28). The apparent superiority of the IV route may be due to the combination of short transport times and a longer time to onset of action for PO medications, and may therefore not be clinically significant.

All patients age >=4 can be treated.
There were few pediatric patients in the study group (66 less than 18 years old, 13 less than 17), but the medication was safe and effective in all ages.

The universal 4 mg dose for all patients was simple to learn and remember, safe, and effective.
This is a common dose used for a similar patient population in emergency department. There were no dose or age-related medication errors.

Ondansetron is needed frequently.
3.7% of the transported patients in March and April were treated with ondansetron. This is similar to a previous report.[1] We chose to analyze the last two whole months of the trial to best approximate the steady-state use of this new medication. By March the drug had been used for several months, was no longer unique, had become standard of care, paramedics were comfortable in its use, and the Hawthorne effect should have diminished. It was felt that this would give a more accurate indication of how frequently this medication would be used going forward and therefore would be more useful for service provider and EMS Agency decision making.

An online database is effective in organizing and managing a multisite study.
The trial study provided a unique opportunity for multiple EMS Agencies and counties to work collectively on a continuous quality improvement (CQI) project utilizing standardized training, policies, protocols, and most notably a uniform CQI process and data collection tool.

7. Recommendations

We recommend that ondansetron be added to the local optional scope of practice as a Category 1 item, and, when the paramedic regulations are next revised, to the statewide scope of practice. Ondansetron is a safe, effective, and frequently indicated medication that substantially improves patient care and reduces suffering.

We also recommend that the EMS Authority investigate mechanisms to make an online database available to LEMSAs and service providers Statewide to facilitate research and QI efforts.

8. References

1. Warden CR, Moreno R, Daya M: Prospective evaluation of ondansetron for undifferentiated nausea and vomiting in the prehospital setting. Prehosp Emerg Care. 2008 Jan-Mar;12(1):87-91.
2. Harold P. Lehmann HP, Fleisher LA, Lam J, et al: Patient Preferences for Early Discharge After Laparoscopic Cholecystectomy. Anesth Analg 1999;88:1280.
3. Zuver C, Silvestri S, Ralls GA, et al: Out-of-hospital use of intravenous ondansetron. Ann Emerg Med. 2007;50(3):S57.
4. Leman P. Utility of ondansetron in children with vomiting. Ann Emerg Med. 2002;40(3):366–7.
5. Reeves JJ, Shannon MW, Fleisher GR: Ondansetron decreases vomiting associated with acute gastroenteritis: a randomized, controlled trial. Pediatrics. 2002;109(4):e62.
6. Freedman SB, AdlerM, Seshadri R, Powell EC: Oral ondansetron for gastroenteritis in a pediatric emergency department. NEJM. 2006;354(16):1698–705.
7. Ramsook C, Sahagun-Carreon I, Kozinetz CA, Moro-Sutherland D: A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. Ann Emerg Med. 2002;39(4):397–403.
8. Stork CM, Brown KM, Reilly TH, Secreti L, Brown LH: Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. Acad Emerg Med. 2006.
9. Gallagher EJ, et al. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med December 2001;38:633-8.
10. Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med December 2001;38:639-43.

APPENDIX A: Training Program Curriculum

(Approximately 90-minute program)

1. Introduction/Study Overview
2. PowerPoint presentation
    a. Study design
    b. Protocols
    c. Pharmacology
    d. CQI process
3. Nausea Scale Tool
4. Written Exam

APPENDIX B: Treatment Protocol

SEVERE NAUSEA/VOMITING PROTOCOL
PARAMEDIC TRIAL STUDY

Indications:
1. Intractable vomiting
2. Severe nausea

Contraindications:
1. Known sensitivity to ondansetron or other 5-HT3 antagonists:
   - Granisetron (Kytril)
   - Dolasetron (Anzemet)
   - Palonosetron (Aloxi)

Objective information:
1. Vital signs
2. Airway Patency
3. Need for antiemetic therapy

Treatment:

Procedure	ALS
Position of Comfort	X
Oxygen	X
Airway Management Protocol	X
Ondansetron: 4 mg IM or slow IV/IM/ODT (IV over > 30 sec) Age 4 yrs and above	X

x = standing order BH/CF = Base Order or Communication Failure

APPENDIX C: QI Form

Ondansetron Trial Study

****Continuous Quality Improvement Data****

Part I: To be completed by treating paramedic

Date:_____ **Incident #:**_____

Call Type (circle): 911 Interfacility Transport Other

Paramedic:_____ **Unit:**_____ **Base Hosp:**_____

Pt Age:_____ **Gender:**_____ **Chief Complaint:**_____

Indication (circle): Vomiting Nausea N/V

 # doses given:_____ **Nausea Scale prior: 1- 10 scale**

Dose #1: _____ **mg Route: IV IM ODT Effect: WORSE (SM/LG) NO CHG BETTER (SM/MOD/LG)**

Dose #2: _____ **mg Route: IV IM ODT Effect: WORSE (SM/LG) NO CHG BETTER (SM/MOD/LG)**

Adverse Effect? Y/N Explain:_____

Comments:_____

_____

Part II: To be completed by Provider CQI Coordinator

Reviewed by:_____ **Date:**_____

Use indicated by protocol?	**Y**	**N**	**Explain:**_____
VS prior/after each dose?	**Y**	**N**	**Explain:**_____
Correct dose?	**Y**	**N**	**Explain:**_____
Correct route?	**Y**	**N**	**Explain:**_____
Effect documented?	**Y**	**N**	**Explain:**_____
Any adverse effects?	**Y**	**N**	**Explain:**_____

Comments:_____

_____

Medical Director comments:_____

Part III: To be completed by EMS Agency CQI Coordinator

Reviewed by:_____ **Date:**_____

Use indicated by protocol?	**Y**	**N**	**Explain:**_____
All documentation completed?	**Y**	**N**	
Agree with Provider CQI Coordinator?	**Y**	**N**	

Comments:_____

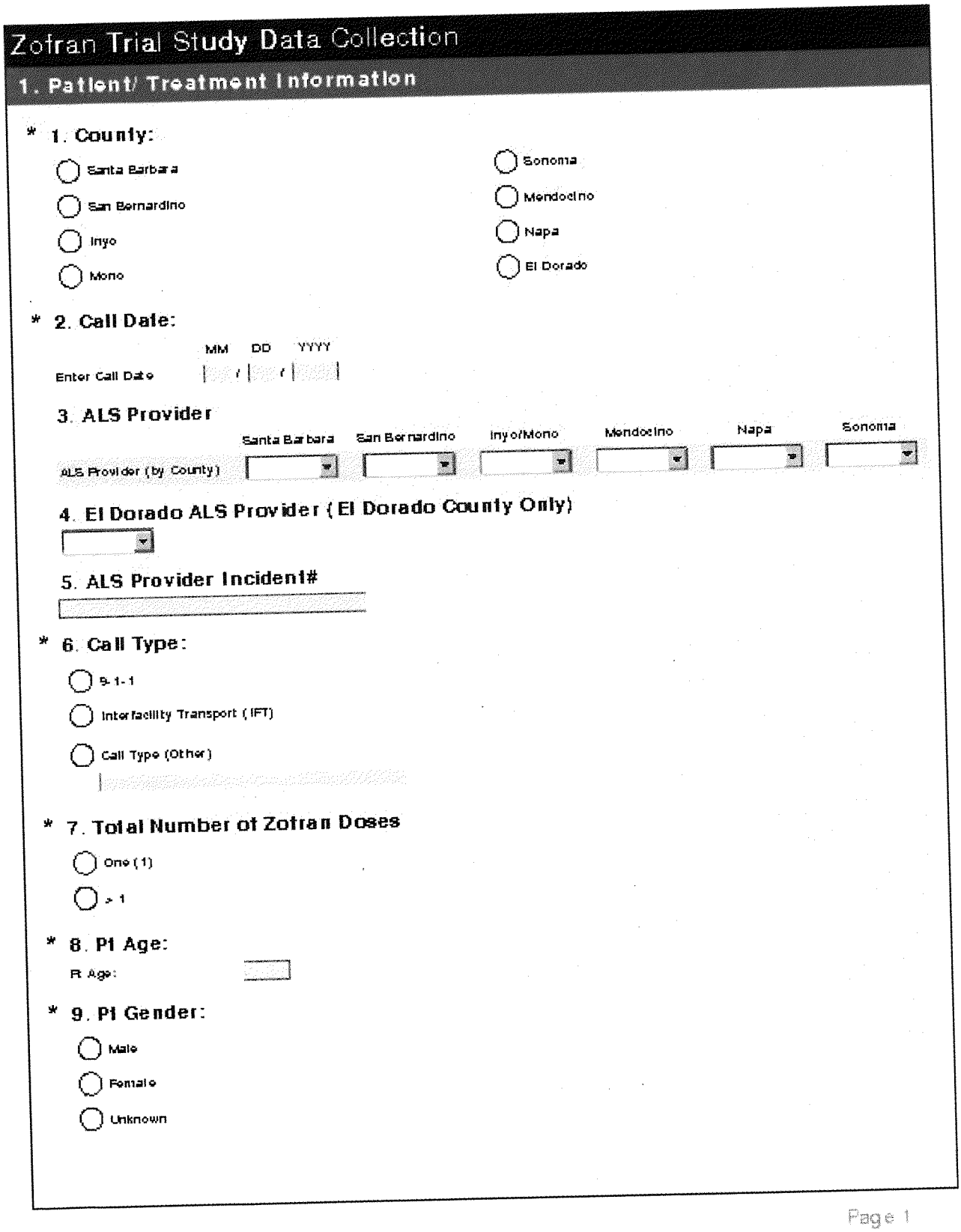
_____

Medical Director comments:_____

All Zofran Trial Study CQI data is to be entered via online data collection tool at:

http://www.surveymonkey.com/s.aspx?sm=B0M0VXAb5S6FHosChgu0zg_3d_3d

APPENDIX D: Data Collection Schema (www.surveymonkey.com)



Zofran Trial Study Data Collection

1. Patient/ Treatment Information

* 1. County:

- Santa Barbara
- San Bernardino
- Inyo
- Mono
- Sonoma
- Mendocino
- Napa
- El Dorado

* 2. Call Date:

Enter Call Date MM / DD / YYYY

3. ALS Provider

	Santa Barbara	San Bernardino	Inyo/Mono	Mendocino	Napa	Sonoma
ALS Provider (by County)						

4. El Dorado ALS Provider (El Dorado County Only)

5. ALS Provider Incident#

* 6. Call Type:

- 9-1-1
- Interfacility Transport (IFT)
- Call Type (Other)

* 7. Total Number of Zofran Doses

- One (1)
- > 1

* 8. Pt Age:

Pt Age:

* 9. Pt Gender:

- Male
- Female
- Unknown

Page 1

Zofran Trial Study Data Collection

* **10. Chief Complaint:**

- ◯ Nausea
- ◯ Vomiting
- ◯ Nausea/Vomiting

* **11. Pre-Medication Nausea Scale Value**

Nausea Severity Scale (1-10) ____

* **12. Initial Dose (mg)**

- ◯ 4 mg
- ◯ Other Dose (Describe) ____

* **13. Initial Dose Route:**

◯ IV ◯ IM ◯ ODT

* **14. Post-Medication Nausea Scale Value (First Dose)**

Nausea Severity Scale (1-10) ____

* **15. Second Dose (mg)**

- ◯ No Second Dose
- ◯ 4 mg
- ◯ Other Dose (Describe) ____

2. Second Dose Data

* **16. Pre-Medication Nausea Scale Value (Second Dose)**

Nausea Severity Scale (1-10) ____

17. Second Dose: Minutes since first dose?

Enter Minutes since for first dose ____

18. Second Dose Route:

◯ IV ◯ IM ◯ ODT

* **19. Post-Medication Nausea Scale Value (Second Dose)**

Nausea Severity Scale (1-10) ____

Zofran Trial Study Data Collection

20. Any additional comments:

3. Provider CQI Review Data

* **21. Reviewed by:**

* **22. CQI Review**

	YES	NO
Indicated By Protocol?	○	○
VS before/after each dose?	○	○
Correct Dose?	○	○
Correct Route?	○	○
Effect documented?	○	○
Adverse Effects?	○	○

23. Describe any adverse reactions or effects:

24. Medical Director Comments:

25. Other additional information:

THANK YOU FOR COMPLETING! YOUR COOPERATION WITH THIS STUDY IS GREATLY APPRECIATED!